Mark B. Feinberg, MD, PhD, FACP
Vice President
Medical Affairs and Policy

Merck & Co., Inc.
WP97-A337
770 Sumneytown Pike
P.O. Box 4
West Point PA 19486
Tel 215 652 8664
Fax 215 652 8918
mark_feinberg@merck.com

January 30, 2009

Bruce Gellin, MD, MPH
Director, National Vaccine Program Office
U.S. Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, SW
Room 715H
Washington, DC 20201–0004

Dear Dr. Gellin:

RE: Draft Strategic National Vaccine Plan

Merck & Co. Inc. commends the Department of Health & Human Services (DHHS) for its commitment to foster innovation while serving the public-health needs of all US citizens and residents. We support US Government activities that are guided by sound scientific principles and evidence-based medical judgment.

In the course of development, licensure, and marketing of our drug and vaccine product candidates, Merck has acquired extensive experience that we used to author the attached comments on the Draft Strategic National Vaccine Plan (November 26, 2008 version) posted at www.hhs.gov/nvpo/vacc_plan/2008plan/draftvaccineplan.pdf.

We thank the Department for the opportunity to comment on the draft Strategic National Vaccine Plan. Merck agrees that although significant successes were achieved following the publication of the 1994 National Vaccine Plan, many challenges remain. Addressing these challenges is critical to realizing the full public health benefits of the national vaccination program.

Our comments focus on **Table 1, Measurable Indicators by Goal in the Draft Strategic National Vaccine Plan**. Our comments are tabulated in the right column of the Table. Where we make no comments, we concur with the indicators as stated.

We provide the following general comments on the entire list of goals and indicators:

- We strongly recommend that the plan provide a detailed implementation plan for the goals and indicators enumerated in the table below and in the plan. The implementation plan should specify agencies with lead responsibility for achieving the goal or sub-goals. In other words, the plan should provide a level of detail more granular than that specified on pages 28 to 61 of the document. Such a level of detail informs clearer thinking that should facilitate successful actualization of the indicators.
- In addition, we recommend that the detailed implementation plan should integrate specific tasks for federal state and local agencies. The plan should also

explicitly call on the agencies to collaborate to achieve the goals and indicators of the Plan.

- For the prioritized list of new vaccines called for in Goal 1 to be meaningful, the agency charged with developing a prioritized list must coordinate and align with the agency responsible for addressing reimbursement issues so that a Goal-1 vaccine would readily receive reimbursement once licensed. Similarly, the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) should synchronize their post-licensure safety assessments, and more clearly delineate which agency has the lead role in various assessment scenarios.

At the end of the document, we list additional editorial and other suggestions to enhance the document.

We appreciate the opportunity to share our thoughts on the Draft Strategic National Vaccine Plan. For further information or questions, please contact me by phone 1-215-652-8664 or email mark_feinberg@merck.com.

Best regards,

Mark Feinberg, MD, PhD, FACP
Vice President, Medical Affairs & Policy

Attachment enclosed

Attachment

Table 1. Measurable Indicators by Goal in the Draft Strategic National Vaccine Plan		
Goal	**Indicator**	**Merck Comments**
Goal 1: Develop new and improved vaccines	Within one year, create an evidence-based list of new vaccine targets to prevent infectious diseases that are high priorities for development.	This indicator is very important. The list should be carefully prioritized based on the public-health burden (current and emergent) of these diseases. The list should be used as the common priority list for activities of all federal agencies. The list should be detailed enough to describe the indication or target population of greatest public-health need, not simply a listing of pathogens by name (e.g., RSV for infants versus elderly). Vaccine needs for the elderly, immunocompromised people, and other subpopulations should be explicitly prioritized. Strategies to achieve this goal should include research to more completely define the epidemiology of a broad range of infectious diseases, to better define these needs. Merck is willing to participate on work groups convened for this task. The United States is underinvested in infectious disease epidemiology. Investments by government to more specifically describe disease burden would reduce uncertainty and help prioritize and assess where public and private investment in vaccine development would be most valuable. Merck would be willing to assist in developing a prioritized list of needs toward addressing broadly useful epidemiology questions and help in study design.
	Identify X candidate vaccines (*e.g.*, for HIV, malaria, TB, and	A time element for this indicator should be added.

	a cross-protective vaccine for influenza) and advance Y priority vaccine candidates along the research and development pipeline including Z candidates into advanced clinical trials.	It may also be useful to cluster candidate vaccines for this purpose into categories (e.g., antibiotic-resistant organisms).
	Advance X new delivery strategies that will improve effectiveness, feasibility, acceptability, safety, or ease of administration of new or improved vaccines into clinical trials.	The meaning of "delivery strategies" should be clarified with examples. Insofar as "delivery strategies" encompasses new adjuvants (which may be critical for protecting special populations such as the elderly), the plan should focus on developing guidance, direction, and support for alternate and innovative adjuvants and immune modulators.
	In X years, have the capability to test potential vaccine candidates in clinical trials developed in response to an emerging infectious disease health threat within six months of the identification of the need for a vaccine.	Capability as used in the indicator may need further definition or quantification. Please clarify what event the 6-month interval is based on (e.g., candidate development, trial development, disease emergence). A timeframe of 6 month may not allow standard preclinical testing and feedback from regulatory agencies prior to clinical testing.
		The United States also needs a highly responsive capability to develop new vaccine candidates rapidly, a step that must occur before clinical trials can begin. Merck and other manufacturers may be able to play a role in this regard, especially in collaboration with the US Government.
		Goal 1 should also reflect the Nation's needs in biosecurity.
		An indicator should be added (under one of the goals of this plan) to ensure that the development of vaccines which may have the effect of benefiting unborn children is not discouraged (e.g., by including those claiming injury due to exposure in

		utero as covered claimants under the National Childhood Vaccine Injury Act, which would also have the effect of allowing such individuals to seek compensation under the VICP).

Goal 2: Enhance the safety of vaccines and vaccination practices	Conduct and disseminate the results of active and passive surveillance-based safety assessments for newly recommended vaccines or for vaccines with expanded recommendations: • Within 1 year of publication in CDC's Morbidity and Mortality Weekly Report of new or revised ACIP recommendations. • Within 1 year after X million doses have been distributed	The national goal must balance speed with quality. Timely results, based on poor quality data or design, do not serve the nation's interests. Results need to be vetted with learned intermediaries (e.g., ACIP work groups) before public release. A consistent method for conducting these assessments and disseminating their results should be developed and implemented. Consider performing assessments at several stages, such as after X million, 2X million, and 4X million doses have been administered. This approach would avoid depending only on a short-interval study that may have an inadequate comparator group (or inadequately understood baseline rates), be inadequately powered, or when reporting may be brisk and rare events may not be identified following initial introduction of the vaccine. The title of Goal 2 is somewhat misleading. The safety profile of a given vaccine is an inherent characteristic that cannot be enhanced. Additional studies could allow better understanding of the safety profile, but the profile, *per se*, cannot be changed. We propose to revise the title to read "Improve the knowledge and understanding of the safety profile of vaccines to enhance vaccination practices."
	Develop and disseminate plans for further investigation, if any, of newly detected AEFI signals and the rationale for those plans within X months of signal detection.	This indicator should focus on the International Conference on Harmonization (ICH) end-to-end (E2E) risk management plan (RMP) for each vaccine (which

		addresses known risks, potential risks, unknown risks). The ICH E2E program exists as a global standard. Good pharmacovigilance practice requires sponsors to have RMPs and procedures in place to identify and investigate emerging safety signals.
		AE report quality: An indicator should be added to increase the proportion of adverse event reports that include the vaccine's lot number, concomitant medications, underlying disease states, and other clinical details that would improve interpretation of vaccine safety data.
	By X year, X % of infants, children, adolescents, adults, and pregnant women will be under active surveillance for AEFIs	The percentages may need to vary for each of the specified cohorts. Rather than stating a percentage goal, consider stating a number of lives for each cohort, based on biostatistical needs, to assess incident events or incidence rates with defined degrees of confidence. Scientifically appropriate control groups are also essential.
	Conduct research to explore host factors and biological mechanisms associated with serious AEFIs and annually report results to the Assistant Secretary for Health, vaccine advisory committees, vaccine policy makers and other stakeholders	Such research is important, but should be approached in a prioritized manner with government involvement.
		An indicator should be added to enhance the ability to conduct controlled, randomized database studies. The US Government should enable more HMOs to establish electronic medical records (EMRs), to permit high-quality collaborative research. With more uniformity and compatibility (to allow

		concatenation), vaccine safety research would be enhanced.
		The US Government should support EMR standards that enhance the ability to conduct effectiveness and safety studies. One objective might be to overcome potential coding biases related to healthcare provider behavior (e.g., when reimbursement rates may influence code selection).
		The US Government should commission studies on the baseline epidemiology of AEFIs that have been associated temporally with vaccines historically (e.g., Guillain-Barré syndrome, myocarditis, unexplained death in young adults).
		The US Government should commission systems research on ways to optimize the quality of data obtained from research using administrative databases (e.g., ability to distinguish between incident and prevalent cases of a specific event or condition).
		The US Government and qualified independent experts should state their conclusions about vaccine safety more forthrightly and clearly describe their advocacy position to enhance the public health benefits of vaccination appropriately, with strong, evidence-based messages understandable by the broad American public.
		The US Government should add an indicator to monitor effectiveness of its efforts to detect and prevent distribution of counterfeit products.

Goal 3: Support informed vaccine decision-making by the public, providers, and policy-makers	Enhance communication with stakeholders and the public to more rapidly inform them (within _X_ days) about urgent and high-priority vaccine and vaccine-preventable disease issues (e.g., outbreaks, supply shortages, vaccine safety concerns).	The document should clearly state the initial time point to be used to calculate the "within X days" interval. The standard should be set carefully, to allow for scenarios where poorly understood situations would have to be reported before adequate guidance to the public could accompany it.
		In addition to more timely communication of "bad news," the US Government should commit to more timely communication of "good news" (e.g., shortening the gap between ACIP decisions and publication in the *MMWR*).
		The US Government should develop processes to more proactively communicate reliable science on disease risks and vaccine benefits and risks to the public, in terms broadly understood by the public, to refute unsubstantiated misconceptions on vaccine safety. Such routine and repeated culturally-appropriate communication will promote educated decision making by individuals.
		Each of the following indicators within Goal 3 would benefit from parallel construction aligned with the Healthy People 2020 objectives, which use a target percentage increase based on a best practice, when available.
	__X__ % of the public will report that they are satisfied with how their health care provider answers their questions	

	about the benefits and risks of vaccines by Y (year).	
	__X__% of the public will report they have access to information which allows them to make informed vaccination decisions for themselves or their children by Y (year).	The US Government should play an active role in providing additional culturally-appropriate educational materials (with varying levels of information content) on the benefits of vaccination in general and that of specific vaccines to the public.
	__X__% of health care providers will report that they have access to accurate and complete information about vaccine benefits and risks and are able to adequately answer questions of parents and patients by Y (year).	
	__X__ % of key decision- and policy-makers will report they have access to vaccine benefits, risks, and costs to make informed decisions about vaccine policy by Y (year).	
	By Y (year) all health professional schools and training programs will include vaccine and vaccine-preventable disease content in their curricula, and assess students' and trainees' knowledge.	These professionals need not just scientific content, but also communication skill training to convey that content to their patients in an understandable way. The US Government should commission development of additional communication curricula to meet this objective.
	By Y (year) all relevant health professional certifying examinations will include vaccine and vaccine-preventable disease questions.	This indicator is important, but we encourage emphasis on curriculum content.

	The United States will have 6 months' supply of all vaccines appropriate to stockpile.	Criteria to define "appropriate to stockpile" should be developed and applied to all vaccines. Some vaccines require more than 6 months to manufacture a single lot, so the inventory level should be developed in an informed manner, recognizing the cycle time for manufacture. This indicator should be reconciled with efforts of the CDC Stockpile Working Group, which endeavors to rationalize stockpile levels.
Goal 4: Ensure a stable supply of recommended vaccines and achieve better use of existing vaccines to prevent disease, disability and death in the United States	Reduce financial and non-financial access barriers, such as cost, availability, culture and language, to immunization by 2020 so that: • _X_% of parents of infants and children report no barriers to immunization; • _X_% of parents of adolescents report no barriers to immunization; and • _X_% of adults report no barriers to immunization.	Merck supports the goal of access to affordable health insurance with vaccination benefits for all. Merck believes this is best attained by strengthening the existing public- and private-sector collaboration on vaccine access and financing that has generally enabled high rates of vaccination, especially for children. Strengthening the system requires recognition of the value of vaccination, adequate fiscal appropriations by governments and private-sector stakeholders (e.g., employers, insurers) to provide sufficient resources for vaccine purchase and administration, and increased attention and resources devoted to adult immunization. Because there are numerous barriers to an optimal system, any solutions will need to be comprehensive to have the desired effect. Other barriers to evaluate include logistical issues (e.g., distance from or transportation to a vaccination provider), societal (e.g., healthcare-delivery models that do not

		prioritize vaccinations programs), and cultural issues (e.g., attitudes toward vaccination).
	Reach or exceed Healthy People 2020 vaccine coverage levels once established, through incrementally increasing coverage rates for pediatric, adolescent and adult populations using coverage levels in 2010 as a baseline.	These are important indicators; it is essential that they address disparities evident based on ethnicity or age. Considering, for example, that pneumococcal 23-valent vaccination levels among adults have plateaued since 2002, considerable extra effort will be needed to reach 2020 goals. Progress toward the Healthy People 2020 goals is the key outcome measure, not the process measures of the preceding indicators.
	X% of electronic health record systems and Y% of immunization information systems will include reminder and recall systems for vaccination by Y (year).	Progress may be more precisely measured by changing the denominator to "lives served by systems."
	Within Y years after its ACIP recommendation, surveillance for at least one major disease outcome for each routinely recommended vaccine will be implemented in X% of states.	We recommend this indicator encompass all States, not just a fraction of them.
	The Vaccine Injury Table is updated as needed (at least every X years).	Consider moving this indicator to Goal 3. If no update to the VIT was needed after X years, which federal official would certify this determination?
		An indicator should be added to enhance the mutual recognition of manufacturing-facility inspectors of certain countries, to avoid diverting industrial resources on redundant inspections. Such mutual recognition should manifest as streamlined, uniform regulatory review with more transparent review guidelines and standards, in a

		way that does not compromise safety.
		US Government efforts to harmonize recommended vaccination schedules among countries would facilitate vaccine development.
		As stated earlier, an indicator should be added (under one of the Goals of this Plan) to overcome liability as a barrier to vaccine development (e.g., in maternal vaccination where a fetus is not covered by liability safeguards).
		An indicator should be added to assess the number of lives (both children and adults) covered by electronic immunization records.
		The US Government should add an indicator to assess and reduce the degree to which the supply chain for imported vaccines (or their components) is vulnerable to disruption overseas in the event of a global or multinational emergency.

Goal 5: Increase global prevention of death and disease through safe and effective vaccination	Transmission of wild polio virus will be eradicated by Y (year).	
	Mortality from measles will be reduced by X% by Y (year) compared with an X (year) baseline.	
	X% of countries will achieve DTP3 vaccination coverage of 90% or greater nationally (and 80% or greater in each country's district) by Y (year).	Districts should be plural.
		Haemophilus influenzae type b, hepatitis B, human papillomavirus, and perhaps other diseases should be added to the indicators.
	Support introduction of new vaccines as part of national vaccination programs: • Meningococcal vaccine in all African countries in the "meningitis belt" by Y (year); • Rotavirus vaccine in X countries by Y (year); and • Pneumococcal conjugate vaccine in Z countries by Y (year).	The list should be prioritized based on public health need. A mechanism should be provided to augment this list, perhaps by linking it to other vaccines provided via Expanded Programme on Immunization (EPI) or an Accelerated Development and Introduction Plan (ADIP) - or GAVI-like process. The US Government should increase its collaboration with international organizations like GAVI and engage in innovative mechanisms to sponsor vaccine development (eg, Advanced Market Commitments, International Finance Facility for Immunization). Merck is willing to work with the US Government on evaluating potential incentives for manufacturers to build capacity to allow these goals to be met more readily. Merck has already committed itself to contributing to vaccine solutions for the developing world.
	X countries establish immunization advisory committees by Y (year)	This indicator might be actualized by means of US

	that make evidence-based decisions on adding new vaccines to the routine program and monitor program quality, vaccination coverage, and vaccine safety.	scientific and technical support to X countries.
	X countries enhance injection safety by Y (year) through the use of auto-disable syringes or other safe injection devices (e.g., needle free delivery) for all immunizations.	The benefits and risks of individual devices such as those named need to be carefully analyzed, including assessment of practicality of their use, to avoid unintended consequences. "All immunizations" may not be an appropriate goal and is not the US standard.
		The US Government should support investment in cold-chain management and vaccine thermostability.
		Countries should be encouraged to develop comprehensive adult immunization programs that should include influenza and pneumococcal infection as target vaccine-preventable diseases.

Suggestions for the Main Text (Draft Strategic National Vaccine Plan, 11/26/08 version):

- Goal 4 (and page 47): The term disability is used where the authors may wish to specify both disability and impairment, which are distinct constructs.
- Page 17, Purpose, Perspective & Scope, second paragraph: The Plan should be aligned with Healthy People 2020 objectives, insofar as national disease outcomes are being assessed.
- Page 19, first full paragraph: Most of the indicators reflect Federal actions, rather than national ones. It may be appropriate to add indicators to assess performance of clinicians, health systems, health payers, and other stakeholders.
- Page 21: "attitude" in first paragraph connotes a subjective nature to vaccine development; recommend deletion.
- Page 25, third paragraph, line 8: Change "ill" to "will."
- Page 29, Strategy 1.4.9: The US Government should provide additional resources to the FDA to permit more frequent communication (e.g., early feedback, consultation during review) and more transparent review (e.g., more consultation and consistent expectations during review) with vaccine sponsors.
- Page 43, Strategy 3.3.3: Add web-based means of dissemination.

- Page 44, Strategy 3.4.1 and elsewhere in the document: Change "parents" to the more inclusive "parents and caregivers."
- Page 44, Strategy 3.4.5: Expand to include discussion of the risks of the relevant diseases, in comparison to the immunizations.
- Page 44, Objective 3.5: A strategy should be added to this objective to inform policy-makers about the economics of vaccine manufacture, on the need to recapitalize manufacturing equipment for existing vaccines from time to time to meet evolving stringent expectations of regulators. An analogy can be found in the utility industry that periodically needs to replace capital equipment.
- Page 45, Objective 3.6: Consider adding communication skills to this objective. Further, it may be useful to cross-reference the HHS Office of Minority Health's national standards for culturally and linguistically appropriate services in health care (www.omhrc.gov/templates/browse.aspx?lvl=2&lvlID=15)
- Page 49, Figure 6: The box labeled "Disease Surveillance" should be shaded.
- Page 49, Strategy 4.1.1: Insert at beginning of sentence "While maintaining high quality and licensure standards..." Further, we suggest changing "two suppliers" to "two sources of supply" (which could be satisfied by a single sponsor) to more readily achieve the desired goal. Another option would be to stockpile bulk vaccine substance, which generally tends to have a longer shelf life than packaged product.
- Page 49, Strategy 4.1.2: Please clarify which vaccine standards need to be harmonized. Presumably these are production standards.
- Page 50, Objective 4.2: Add a strategy that calls for support to the existing system of private-sector vaccine providers, providing them the tangible and intangible resources needed to sustain this form of vaccine delivery.
- Page 50, Strategy 4.2.1: Insert "required" in front of "by publicly funded health insurance plans..." to complete the thought.
- Page 50, Strategy 4.2.5: Insert "and storage" after "for purchase..." to complete the context.
- Page 52, Strategy 4.4.5: Change "Monitor" to "Conduct studies to assess..."
- Page 52: Add Strategy 4.4.7, Support the development and implementation of a web-based reportable disease notification system.
- Page 53, Strategy 4.5.8 and elsewhere in document: Change "compliance" to "adherence"
- Page 54, Strategy 4.8.2: Insert "and regulations" after "state immunization laws..." Insert "pre-school," after "childcare...."
- Page 54, Strategy 4.8.3: Change "Plan" to "Prepare"
- Page 56, Goal 5: The US Government should collaborate more with US-based industry in its efforts to improve global health.
- Page 60, Strategy 5.3.3: Change "vaccine" to "vaccines"
- Page 60, Strategy 5.4.2: Insert "culturally appropriate," after "transparent..."

- Page 61, Strategy 5.4.6: Insert "and professionals" after "scientists…"
- Page 61, Strategy 5.5.4: Insert ", in accordance with current Good Manufacturing Practices" at end of sentence (to mimic Strategy 5.5.2).
- Page 64, Appendix, on Pneumococcal Vaccination: Revise last bullet that inaccurately characterizes the benefits of adult vaccination of pneumococcal vaccination (with polysaccharide vaccine)
- Page 65, Appendix in row with heading "Some vaccines requiring multiple doses…": Suggest the wording "has not affected access to immunization" be removed or softened in light of publications describing better vaccination coverage with use of combination vaccines (Marshall GS et al. Pediatric Infect Dis J 2007; 26 (6):496-500.
- Page 65: In line with above, also do not agree that no evidence of cost effectiveness for combination vaccines